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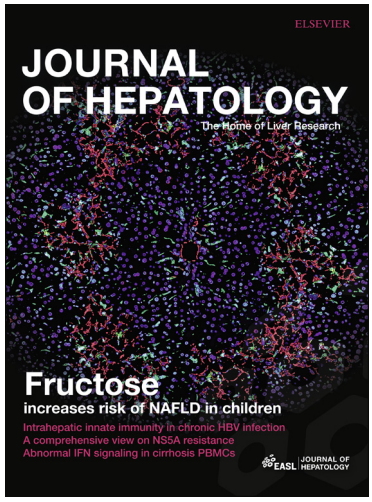

Letter to the Editor

Studies of macrophage therapy for cirrhosis – from mice to men

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Title page:

Letter to Editor re Ma et al (Cytotherapy with M1-polarized macrophages ameliorates liver fibrosis by modulating immune microenvironment in mice. J Hepatol. 2017 Oct;67(4):770-779).

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Title: Studies of macrophage therapy for cirrhosis – from mice to men

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Studies of macrophage therapy for cirrhosis – from mice to men

We read with interest the recently published paper by Ma et al. (1) in which they examined the effects of macrophage infusion in experimental liver fibrosis. The beneficial effects on measures of liver scarring and regeneration following the delivery of bone marrow derived macrophages (BMDMs) suggest clinical potential.

BMDMs injected during iterative liver injury resulted in the hepatic engraftment of relatively few donor cells. Consistent with our previously reported findings (2), macrophage administration resulted in modulation of the host immune response with upregulation of antifibrotic matrix metalloproteinases, apoptosis of scar producing myofibroblasts and subsequent reduction in liver fibrosis. The injection of unpolarized (naïve) BMDMs mediated these effects as did those previously stimulated *in vitro* to a classical "M1" phenotype. In contrast, BMDMs activated to the alternative "M2" phenotype were not beneficial.

Our group's work characterizing the "restorative macrophage" during the spontaneous regression of fibrosis after liver injury, has shown that these phagocytic Ly6C^{lo} cells do not conform to the traditional M1-M2 paradigm (3). The hepatic macrophage population extracted from recipient liver after BMDM therapy in this paper appeared to have a comparable phenotype. This could indicate that BMDM therapy is able to harness this endogenous repair process, critically, in the context of ongoing liver injury. The demonstrated upregulation of macrophage chemokines (CCL-2 and -3) is consistent with the hepatic recruitment of host cells. Amplification of the effects of the initial cell injection through paracrine signaling is an attractive concept to explain the enduring changes found weeks after BMDM delivery. However, this does not exclude a significant contribution to the increased numbers of hepatic F4/80+ macrophages from proliferation of resident hepatic macrophages in addition to recruitment (4).

Ma et al. (1) also demonstrated that BMDM infusion increased the number of activated hepatic NK cells, with the potential to promote myofibroblast apoptosis. Whether this NK cell enrichment reflects a direct effect of the infused BMDMs or a consequence of the modulation in host macrophage phenotype remains to be elucidated. Further studies, administering BMDMs deficient in specific chemokines could provide further mechanistic insights.

We have reported increased serum albumin levels following BMDM therapy (2). This finding has also been recapitulated by Ma et al. (1). The increase in Ki67+ hepatocytes identifies hepatocyte proliferation as a regenerative mechanism after BMDM delivery. Our work exploring BMDM therapy mediated regeneration in both the injured (2) and uninjured (5) liver has also indicated a role for the liver progenitor cell (LPC) mitogen TWEAK. This cytokine specifically activates the LPC compartment thereby increasing liver cell mass. Evaluation of this axis following injection of differentially polarized macrophages would be informative from biological and translational perspectives.

The authors also tested BMDM therapy in cholestatic fibrosis due to bile duct ligation. The antifibrotic effect was found to be of a similar magnitude to that detected in the carbon tetrachloride (CCl_4) induced model of hepatitic injury. The mechanistic studies reported in this article were carried out exclusively in the CCl_4 model. We have previously demonstrated fundamental differences in the spatial and in turn functional characteristics of biliary versus hepatitic fibrosis and regeneration (6). Therefore, further exploration of the processes underlying the effects observed in this cholestatic model will be of great interest.

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Following our initial report (2), we have sought to test the translational potential of BMDM therapy. Human macrophages injected into mice with experimental liver fibrosis showed similar positive effects on liver fibrosis and function (7). Building on this infrastructure, our group has validated and scaled-up a Good Manufacturing Practice-compliant process for deriving human macrophages for therapy (8). A first in man study of autologous macrophage infusion in cirrhosis (ISRCTN 10368050) has already commenced to determine whether these promising pre-clinical findings can yield effective treatment for patients with cirrhosis.

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